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Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis

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The role of steroid treatment in drug-induced acute interstitial nephritis (DI-AIN) is controversial. We performed a multicenter retrospective study to determine the influence of steroids in 61 patients with biopsy-proven DI-AIN, 52 of whom were treated with steroids. The responsible drugs were antibiotics (56%), non-steroidal anti-inflammatory drugs (37%) or other drugs. The final serum creatinine was significantly lower in treated patients while almost half of untreated patients remained on chronic dialysis. Among treated patients, over half showed a complete recovery of baseline renal function, whereas the rest remained in renal failure. There were no significant initial differences between these two subgroups in terms of duration or dosage of steroids. After withdrawal of the presumed causative drug, we found that when steroid treatment was delayed (by an average of 34 days) renal function did not return to baseline levels compared to those who received steroid treatment within the first 2 weeks after withdrawal of the offending agent. We found a significant correlation between the delay in steroid treatment and the final serum creatinine. Renal biopsies, including three patients who underwent a second biopsy, showed a progression of interstitial fibrosis related to the delay in steroid treatment. Our study shows that steroids should be started promptly after diagnosis of DI-AIN to avoid subsequent interstitial fibrosis and an incomplete recovery of renal function.

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Drug-induced acute interstitial nephritis (DI-AIN) represents a significant cause of acute renal failure (ARF) in hospital practice.[1,2] As reported in some studies, about 15% of the renal biopsies performed in patients with ARF demonstrated a DI-AIN as the cause of the renal insufficiency.[3] Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently implicated agents, but the list of drugs that can induce a DI-AIN is continuously increasing.[1] A general agreement exists about the discontinuation of the offending drug as the first therapeutic step in patients with DI-AIN. However, although renal function improves in a majority of patients after this measure, serum creatinine (Scr) does not return to its baseline value in a significant proportion of cases.[1,4]

Controversy persists about the role of steroids in the treatment of DI-AIN. Whereas some studies have reported a more rapid and complete recovery of baseline renal function in those patients treated with steroids,[5–7] others have failed to confirm these results.[8–10] Available information about the treatment of DI-AIN is based only on numerous case reports and observational series including a short number of cases. The absence of large retrospective series or prospective controlled studies is the main cause of the inconsistency of data regarding the most appropriate treatment for DI-AIN.

In this retrospective multicenter study, we analyzed the influence of steroid treatment and other factors that could influence the long-term outcome of DI-AIN. We gathered 61 patients with biopsy-proven DI-AIN, the largest series studied so far. All the patients had a known baseline Scr and all of them were followed during a period of time sufficient to adequately establish their long-term outcome. We found that steroid treatment induced a significant beneficial effect on the normalization of renal function. Furthermore, we found that a delay in the onset of steroid treatment after discontinuation of the responsible drug was the most significant factor to determine an incomplete recovery of baseline Scr.

RESULTS

A total of 61 biopsy-proven DI-AIN were analyzed. Demographic and clinical characteristics are expressed in Table 1. All the patients had a baseline Scr (1.1 ± 0.39; range 0.4–2.3 mg per 100 ml) obtained 7.5 ± 4.6 (range 0.5–16) months before the onset of DI-AIN. Baseline estimated glomerular filtration rate (eGFR) was 71 ± 25 (range 35–151 ml per min per 1.73 m^2). Twenty-two patients (36%) had a baseline eGFR lower than 60 ml per min per 1.73 m^2. The drug responsible for the DI-AIN episode was identified as an antibiotic in 34 patients (56%) (cephalosporins in 15 patients, quinolones in 12, and penicillins in 7), NSAIDs in 23 (37%), and other drugs (allopurinol, omeprazole, ranitidine, and pimozide) in the remaining four patients.

As expressed in Table 1, most of the patients presented some of the classic clinical characteristics of DI-AIN (fever, maculopapular rash, eosinophilia) with declining renal function, although only eight patients (13%) showed these three characteristics together. No significant differences in the incidence of rash and fever were observed between DI-AIN related to antibiotics, NSAIDs, and other drugs. Eosinophilia was significantly less common among patients with DI-AIN secondary to NSAIDs (18 vs 44% in DI-AIN not related to NSAIDs, $P < 0.05$). Most of the patients (40/61, 65%) showed proteinuria, ranging from 0.4 to 6 g/24 h, and abnormalities in the urinary sediment (microhematuria in 67% and leukocyturia in 82%). Baseline proteinuria was significantly higher in DI-AIN related to NSAIDs (1.4 ± 1.4 g/24 h) in comparison with DI-AIN secondary to other drugs (0.7 ± 0.8 g 24 h^{-1}; $P = 0.05$). Highest Scr oscillated between 1.5 and 13.3 mg per 100 ml with a mean of 5.7 ± 3.3 mg per 100 ml. Fourteen (23%) patients needed several sessions of hemodialysis due to the severity of their ARF.

Table 1 | Clinical characteristics of the patients

Characteristic	Value
Age (years)	57.7 ± 17.4 (range 18–81)
Gender (M/F)	39/22
Baseline Scr (mg per 100 ml)	1.1 ± 0.39 (range 0.4–2.3)
Baseline eGFR (ml per min per 1.73 m^2)	71 ± 25 (range 35–151)
Highest Scr (mg per 100 ml)	5.7 ± 3.3 (range 1.5–13.3)
Oliguria	14 (23%)
Skin rash	14 (23%)
Fever	26 (42%)
Eosinophilia (> 500 eosinophils/mm^3)	21 (34%)
Proteinuria (g/24 h)	0.9 ± 1.1 (range 0–6)
Microhematuria	41 (67%)
Leukocyturia	50 (82%)

eGFR, estimated glomerular filtration rate; F, female; M, male; Scr, serum creatinine.

Comparison between patients treated (Group 1) and untreated (Group 2) with steroids

Fifty-two patients were treated with steroids 23 ± 17 (range 2–68) days after the withdrawal of the offending drug (Group 1). Although steroid doses and duration of the treatment were not uniform due to the multicenter character of the study, the most common scheme of treatment consisted of intravenous pulses of methylprednisolone (250–500 mg daily for 3–4 consecutive days) followed by oral prednisone (1 mg/kg/day) tapering off over 8–12 weeks. The remaining nine patients did not receive steroids (Group 2). As expressed in Table 2, there were no differences in baseline characteristics (age, gender, baseline Scr and eGFR, type of offending drug, duration of treatment, highest Scr and proteinuria, or the interval between the withdrawal of the responsible drug and the performance of renal biopsy) between Group 1 and Group 2 patients. The final outcome of Group 1 patients (steroid treatment) was significantly better than that of Group 2 (no steroid treatment); as shown in Table 2, final Scr was significantly lower in Group 1 patients and a significantly higher proportion of Group 2 patients remained on chronic dialysis after the DI-AIN episode (44.4 vs 3.8%). No side effects attributable to steroid treatment were observed.

Comparison between steroid-treated patients who showed a complete (Group 1a) or an incomplete (Group 1b) recovery of baseline renal function

Twenty-eight out of 52 patients in Group 1 showed a complete recovery of baseline renal function after steroid treatment (Group 1a), whereas in the remaining 24 patients (Group 1b) renal function did not reach the baseline values. As expressed in Table 3, there were no significant differences

Table 2 | Characteristics of Group 1 (steroid treatment) and Group 2 (no steroid treatment)

	Group 1 (*n*=52)	Group 2 (*n*=9)	*P*-value
Age (years)	57.6 ± 17.5	58.1 ± 18	NS
Gender (M/F) (%)	61.5/38.5	77.8/22.2	NS
Baseline Scr (mg per 100 ml)	1.14 ± 0.4	1.13 ± 0.37	NS
Baseline eGFR (ml per min per 1.73 m^2)	71 ± 26	70 ± 25	NS
Offending drug (antibiotics/NSAIDs/others) (%)	53.8/34.6/11.5	66.7/33.3/0	NS
Duration of the treatment (days)	13.4 ± (r 3–60)	12.6 ± (range 4–30)	NS
Highest Scr (mg per 100 ml)	5.9 ± 3.4	4.9 ± 2.1	NS
Proteinuria (g/24 h)	1 ± 1.2 (range 0–6)	0.6 ± 0.6 (range 0–1.7)	NS
Complete recovery of renal function	28 (54%)	3 (33%)	NS
Chronic dialysis	2 (3.8 %)	4 (44.4 %)	< 0.001
Final Scr (mg per 100 ml)	2.1 ± 2.1 (range 0.7–12.7)	3.7 ± 2.9 (range 0.7–8.9)	< 0.05
Follow-up (months)	19 ± 19 (range 6–60)	18 ± 18 (range 6–56)	NS

eGFR, estimated glomerular filtration rate; F, female; M, male; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; Scr, serum creatinine.

Table 3 | Characteristics of steroid-treated patients with a complete (Group 1a) or incomplete (Group 1b) recovery of baseline renal function

	Group 1a (n=28)	Group 1b (n=24)	P-value
Age (years)	55 ± 18 (range 18–78)	60 ± 16 (range 18–81)	NS
Gender (M/F) (%)	61/39	62/38	NS
Baseline Scr (mg per 100 ml)	1.07 ± 0.31 (range 0.6–1.9)	1.20 ± 0.4 (range 0.6–2.3)	NS
Baseline eGFR (ml per min per 1.73 m^2)	77 ± 29 (range 36–151)	65 ± 21 (range 35–106)	NS
Offending drug (antibiotics/NSAIDs/other) (%)	57/29/14	50/50/0	NS
Duration of the treatment (days)	11 ± 7 (range 3–35)	16 ± 16 (range 5–60)	NS
Highest Scr (mg per 100 ml)	5.3 ± 3.5 (range 1.5–13.3)	6.4 ± 3.3 (range 2.9–12.7)	NS
Proteinuria (g/24 h)	1.1 ± 1.4 (range 0–6)	0.9 ± 0.8 (range 0–3.4)	NS
Final Scr (mg per 100 ml)	1.1 ± 0.26 (range 0.7–1.8)	3.23 ± 2.7 (range 1.5–12.7)	<0.0001
Chronic dialysis	0	2 (8.3%)	NS
Interval between drug withdrawal and onset of corticosteroid treatment (days)	13 ± 10 (range 2–53)	34 ± 17 (range 3–68)	<0.0001
Patients with an interval between drug withdrawal and onset of corticosteroid treatment <7 days	10 (35.7%)	2 (8.3%)	<0.05
Patients with an interval between drug withdrawal and onset of corticosteroid treatment <15 days	19 (67.9%)	2 (8.3%)	<0.05
Duration of steroid treatment (days)	75 ± 37 (range 20–180)	78 ± 42 (range 16–165)	NS
Follow-up (months)	16 ± 17 (range 6–60)	24 ± 20 (range 6–63)	NS

eGFR, estimated glomerular filtration rate; F, female; M, male; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; Scr, serum creatinine.

in the baseline characteristics of Group 1a and Group 1b patients, although baseline renal function tended to be worse and mean age older in Group 1b in comparison with Group 1a. Duration of the treatment with the offending drug was longer in Group 1b, but this difference did not reach statistical significance. Duration of steroid treatment was similar in both groups, but the onset of steroid treatment after drug withdrawal was significantly delayed in Group 1b (34 ± 17 vs 13 ± 10 days in Group 1a, $P<0.0001$) as shown in Table 3. The proportion of patients who received steroids within the first 7 days and 15 days after the withdrawal of the responsible drug was significantly higher in Group 1a than in Group 1b are as follows: 35.7 vs 8.3%, $P<0.05$ and 67.9 vs 8.3%, $P<0.0001$, respectively (see Table 3). By multiple logistic regression analysis, an interval longer than 7 days between drug withdrawal and onset of steroid treatment (odds ratio (OR) 6.6; 95% confidence interval (CI) 1.3–33.6, $P=0.02$) and the severity of interstitial fibrosis (OR 14.5; 95% CI 3.4–61, $P=0.0001$) were the only clinical factors that significantly increased the risk of an incomplete recovery of renal function, whereas other clinical and analytical variables such as age, gender, baseline Scr and eGFR, and highest Scr or baseline had no significant influences.

As shown in Figure 1, significant correlation between the delay in the onset of steroid treatment after drug withdrawal and the final Scr was observed ($r=0.45$, $P<0.005$). Recovery of renal function, expressed by a >50% Scr decrease with respect to the highest Scr, was significantly faster in Group 1a as shown in Figure 2.

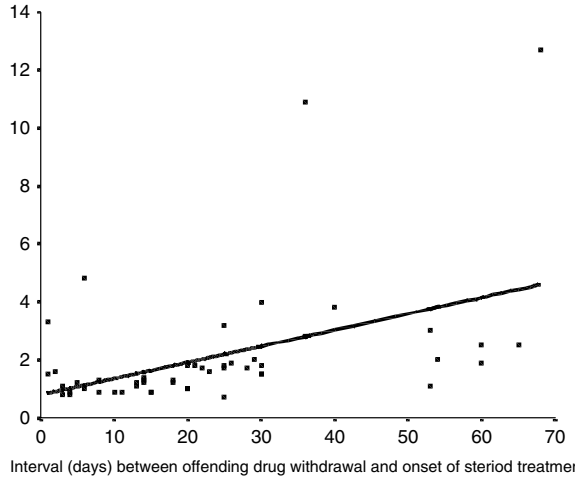

Figure 1 | Correlation between the delay in steroid treatment and final Scr.

Histologic findings

A renal biopsy was obtained in all patients, although the interval between drug withdrawal and its performance oscillated widely. In all cases, a diffuse infiltration of inflammatory cells composed of lymphocytes, eosinophils, monocytes, and plasma cells into the interstitial compartment was observed. Occasional focus of tubulitis was observed. No correlation between the type of offending drug and the histologic findings was observed. Peripheral eosinophilia did not correlate with the number of eosinophils infiltrating renal interstitium. Renal biopsies were always performed shortly before the onset of steroid treatment in those patients who were treated. The main histologic findings are shown in Table 4. The severity of diffuse cellular infiltrates, as well as their composition, was similar in all the patients. However, differences were found in the degree of interstitial and glomerular sclerosis. Main histologic findings are shown in Table 4. Although there was a tendency to a more severe interstitial fibrosis and glomerular sclerosis among Group 2 patients, this difference did not reach statistical significance.

A longer interval between drug withdrawal and the performance of renal biopsy as well as a greater severity of interstitial fibrosis were found in Group 1b (who did not

completely recover baseline renal function in spite of steroid treatment) in comparison with Group 1a (Table 4).

A second renal biopsy was performed in three patients (two patients of Group 1b and one patient of Group 2) 33 ± 7 (range 26–40) days after the performance of the first biopsy. In the three cases, the interstitial cellular infiltrates observed in the first biopsy showed a considerable size reduction in the second biopsy. By contrast, large areas of interstitial fibrosis, not observed in the first specimens, were prominent in the second ones. Histologic changes between first and second biopsy are illustrated in Figure 3.

Patients with DI-AIN due to NSAIDs

In 23 patients the drug responsible for the DI-AIN episode was identified as an NSAID. We applied to these patients the same definitions and statistical analysis performed in the whole group of patients. Twenty patients were treated with steroids; nine of them showed a complete recovery of baseline renal function (NSAIDs-Group 1a), whereas in the remaining 11 patients renal function did not reach the baseline values (NSAIDs-Group 1b). Characteristics of both subgroups are shown in Table 5. There were no significant differences in the baseline characteristics of both subgroups. As in the whole group of patients, the main difference was the interval between NSAID withdrawal and onset of steroid treatment, which was significantly delayed in Group 1b patients (31.4 ± 15 vs 18.4 ± 16 days ($P<0.05$). The proportion of patients who received steroids within the first 15 days after withdrawal of the NSAIDs was significantly higher in NSAID-Group 1a than in NSAID-Group 1b: 44 vs 9.1% ($P<0.05$).

In the three NSAID-induced DI-AIN patients who did not receive steroids, baseline Scr was 1 ± 0.3 (range 0.7–1.3) mg per 100 ml. Their final Scr was 1.9 ± 1.1 (range 0.7–2.6) mg per 100 ml.

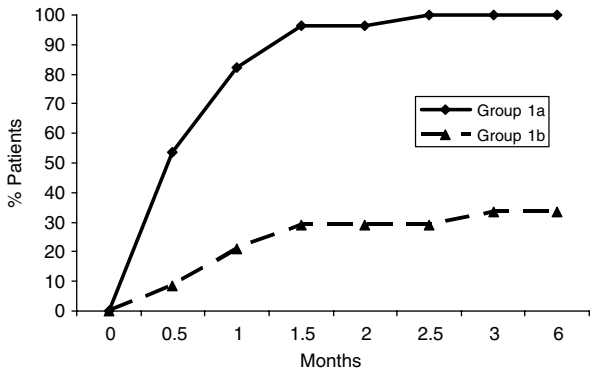

Figure 2 | Rate of renal function recovery, expressed by a >50% decrease of highest Scr, in Group 1a (final complete recovery of renal function) and Group 1b (incomplete recovery).

DISCUSSION

The role of steroids in the treatment of DI-AIN remains controversial. Despite the importance of this entity as a

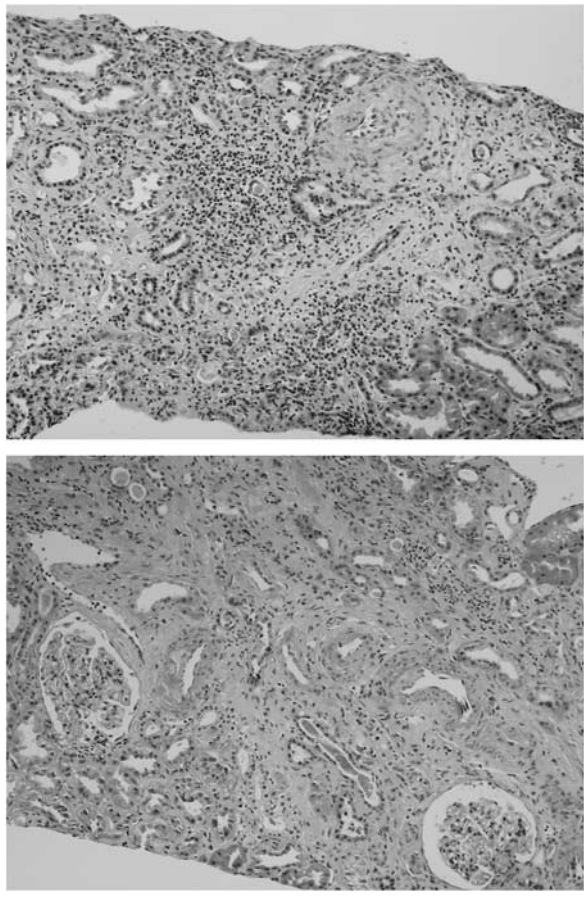

Figure 3 | Evolution of interstitial infiltrates. Dense interstitial cellular infiltrates in the first renal biopsy of a patient of Group 1b (top). In a second renal biopsy, obtained 33 days later, cellular infiltrates have been largely replaced by fibrotic areas in the interstitium (bottom).

Table 4 | Histologic findings

	Group 1	Group 2	*P*-value	Group 1a	Group 1b	*P*-value
Interval between drug withdrawal and renal biopsy (days)	22 ± 17 (range 1–65)	26 ± 24 (range 7–75)	NS	13 ± 10 (range 1–53)	33 ± 17 (range 1–65)	<0.0001
Interstitial fibrosis						
Mild	32 (61.5%)	4 (44%)	NS	25 (89.3%)	7 (29.2%)	<0.0001
Moderate	14 (27%)	2 (22.2%)		3 (10.7%)	11 (45.8%)	
Severe	6 (11.5%)	3 (33%)		0	6 (25%)	

Table 5 | Patients with DI-AIN due to NSAIDs treated with steroids

	NSAIDs-Group 1a (*n*=9)	NSAIDs-Group 1b (*n*=11)	*P*-value
Age (years)	51 ± 24 (range 18–78)	61.2 ± 16 (range 24–81)	NS
Gender (M/F) (%)	66.7/33.3	45.5/54.4	NS
Baseline Scr (mg per 100 ml)	1 ± 0.39 (range 0.6–1.9)	1.1 ± 0.46 (range 0.6–2.3)	NS
Baseline eGFR (ml per min per 1.73m^2)	83 ± 37 (range 36–151)	70 ± 25 (range 35–106)	NS
Duration of NSAIDs treatment (days)	12.4 ± 10.9 (range 3–35)	25.4 ± 20.4 (range 7–60)	NS
Highest Scr (mg per 100 ml)	3.8 ± 1.7 (1.5–7.7)	5.2 ± 2.7 (range 3.1–12)	NS
Proteinuria (g/24 h)	1.8 ± 2.2 (range 0.33–6)	1.3 ± 1 (range 0.1–3.4)	NS
Final Scr (mg per 100 ml)	1.1 ± 0.3 (range 0.7–1.6)	2.4 ± 1 (range 1.6–4.8)	<0.0001
Chronic dialysis	0	1 (9.1 %)	NS
Interval between NSAIDs withdrawal and onset of corticosteroid treatment (days)	18.4 ± 16 (range 2–53)	31.4 ± 15 (range 6–60)	<0.05
Patients with an interval between NSAIDs withdrawal and onset of corticosteroid treatment <7 days	3 (33 %)	1 (9.1 %)	NS
Patients with an interval between NSAIDs withdrawal and onset of corticosteroid treatment <15days	5 (44 %)	1 (9.1 %)	<0.05
Duration of steroid treatment (days)	91.5 ± 49.9 (range 20–180)	75.4 ± 42 (range 30–180)	NS
Follow up (months)	30 ± 24.5 (range 6–60)	21.3 ± 17 (6–60)	NS

DI-AIN, drug-induced acute interstitial nephritis; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; NSAIDs-Group 1a, complete recovery of baseline renal function. NSAIDs-Group 1b, incomplete recovery.

frequent cause of ARF,[1–3] no prospective studies have investigated the possible beneficial effect of steroids on DI-AIN. Some studies have suggested a positive influence, by showing a quicker and complete recovery of renal function in those patients who received steroids.[5–7] However, other studies have failed to confirm these results.[8–10] Thus, in the largest series so far published, Clarkson *et al.*[10] reported 60 patients with acute interstitial nephritis. More than 90% of the patients had a DI-AIN and NSAIDs were the most common etiology, accounting for 44% of cases. In this study, no differences were found regarding final Scr among those patients who received steroids and those who received only conservative management. It should be considered, however, that steroid treatment was considerably delayed, and that, although not statistically significant, baseline Scr tended to be higher among patients who were not treated with steroids.

On the basis of the available evidence, several reviews recommend the use of steroids in DI-AIN only in those patients in whom renal function does not recover after an observational period of 7–15 days after the removal of the offending drug.[1] Nevertheless, many studies show that a significant proportion of patients suffering DI-AIN do not completely achieve their baseline renal function, persisting with different degrees of chronic renal insufficiency after the acute damage.[1,4]

Our study provides the largest series of biopsy-proven DI-AIN gathered so far: 61 patients. Although the data were retrospectively collected, advantages of the study were the knowledge of the baseline renal function in all the included patients and a follow-up sufficiently long to ascertain the final outcome of every patient. We observed that the few patients (9 out of 61, Group 2) who did not receive steroids showed a final Scr significantly higher, and the proportion of patients entering into chronic dialysis was significantly higher than those who were treated with steroids (Table 2). Furthermore, when analyzing the outcome of steroid-treated patients, we found that some of them had completely recovered their baseline renal function (Group 1a), whereas the remaining (Group 1b) persisted with different degrees of chronic renal insufficiency, despite an initial improvement of renal function after the withdrawal of the causative drug. The most salient difference between both subgroups was the interval between drug withdrawal and the onset of steroid treatment: 13 ± 10 days in the former and 34 ± 17 days in the latter (Table 3). In addition, we found a significant correlation between the delay in the onset of steroids and the final Scr (Figure 1), and that an interval longer than 7 days between drug withdrawal and onset of steroid treatment was the only clinical factor that significantly increased the risk of an incomplete recovery of renal function by multiple logistic regression analysis.

Therefore, our study strongly suggests that steroid treatment is indicated in DI-AIN and that it should be started immediately or soon after the diagnosis to avoid the risk of incomplete renal function recovery. No significant side effects attributable to steroids were observed, probably due to the short duration of the treatment (8–12 weeks).

We think that this latter point has not been sufficiently emphasized in the previous literature, because most of the patients with DI-AIN started to improve after the withdrawal of the offending drug. However, as several previous studies have pointed out and our study confirms, this initial improvement is frequently exhausted and many patients will exhibit chronic renal insufficiency as a consequence of a DI-AIN episode. Recent studies have stressed the importance of an even mildly reduced renal function, both in terms of a future progression into end-stage renal failure and of an increased risk of cardiovascular events.[11]

The rationale for an early institution of steroids in DI-AIN is illustrated by the histologic findings of our study (Table 4).

Steroid treatment was initiated after the performance of a renal biopsy in all Group 1 patients. However, the interval between drug withdrawal and the performance of renal biopsy was significantly longer in Group 1b patients (with incomplete recovery of renal function) than in Group 1a patients. Although the typical histologic findings of DI-AIN (diffuse infiltration of lymphocytes, monocytes, plasma cells, and eosinophils into the interstitial compartment) were observed in every case, the severity of interstitial fibrosis was significantly worse in Group 1b patients. These findings suggest that interstitial infiltrates characteristic of DI-AIN are rapidly replaced by irreversible interstitial fibrosis and that early steroid treatment could avoid this fibrotic process by decreasing the severity of interstitial cellular infiltrates, perhaps in a way similar to that of interstitial infiltrates of acute rejection treated with steroids. Even more illustrative are the three cases in whom a second renal biopsy was performed 33 ± 7 (range 26–40) days after the first biopsy. A considerable size reduction of the interstitial cellular infiltrates, which had been largely replaced by interstitial areas of fibrosis, was observed (Figure 3). We think that the histologic evolution of these patients is very interesting because very few iterative biopsies have been published in DI-AIN and it demonstrates that interstitial cellularity is rapidly replaced (in the absence of steroid treatment) by extensive fibrosis in a few weeks.

Some studies have suggested that DI-AIN caused by NSAIDs could have a worse prognosis and a poorer response to steroid treatment.[12,13] We analyzed separately the outcome of our patients with DI-AIN due to NSAIDs (Table 5). The results were similar to those of the whole group, showing that the delay in the onset of steroids was again the most important determinant of an incomplete recovery of baseline renal function. In those patients with DI-AIN due to NSAIDs who achieved the baseline renal function after steroid treatment, steroids were started 18.4 ± 16 days after NSAIDs withdrawal, an interval significantly shorter than in the group that did not recover completely their baseline function (31.4 ± 15 days).

In conclusion, our data strongly suggest a beneficial influence of steroids on the outcome of DI-AIN. Furthermore, according to our results, steroids should be started immediately after the diagnosis of DI-AIN is established to avoid the progressive replacement of interstitial cellular infiltrates by interstitial fibrosis.

MATERIALS AND METHODS

We performed a retrospective analysis of patients with biopsy-proven DI-AIN studied in 10 hospitals of the Comunidad de Madrid in the period 1975–2006. The clinical suspicion of DI-AIN was based on the presence of an acute renal function deterioration chronologically related to a determined drug and accompanied by some signs and symptoms characteristics of DI-AIN: fever, maculopapular rash, eosinophilia, proteinuria, and urinary sediment abnormalities (sterile leukocyturia, hematuria). The diagnosis of DI-AIN was confirmed by a renal biopsy in all the patients included in the study. Histologic diagnosis of DI-AIN was established in the presence of a diffuse infiltration of inflammatory cells into the interstitial compartment with sparing of glomeruli and accompanied by different degrees of interstitial edema and fibrosis. The infiltrating cell population was composed of lymphocytes, monocytes, plasma cells, and eosinophils. Patients with clinical or analytical data that suggested systemic diseases were excluded. Three patients with granulomatous DI-AIN were excluded because of the suspicion of sarcoidosis in two and Sjögren syndrome in one.

The presence of urinary tract obstruction or other urinary tract abnormalities was excluded by appropriate radiological examinations. In all the patients, the presence of urinary tract infection, including renal tuberculosis, was ruled out by urine cultures.

Medical records of the patients were reviewed for this study. All the patients had been admitted to the hospital during DI-AIN and were discharged when renal function started to improve or stabilize. Once identified, the responsible drug was withdrawn in all patients. In those patients with antibiotic-related DI-AIN, alternative antibiotic therapy was introduced, if indicated, after the removal of the offending drug. A majority of patients, but not all, were treated with corticosteroids. The interval between the withdrawal of the responsible drug and the onset of steroid treatment in those patients who were treated was variable. Steroids were started after the performance of renal biopsy in all the patients.

After discharge, all patients were followed at regular intervals (usually every 2 weeks in the first visits and thereafter every 6 months once Scr remained stable). The following data at admission were obtained from medical records and analyzed for this study: age, gender, blood pressure, abnormal findings on physical examination, and complete baseline treatment. Analytical study included a complete blood count, routine serum biochemistry profile, urine sediment examination, urine cultures, and 24-h proteinuria. Evolution of these analytical parameters during admission and thereafter during follow-up was also recorded. Estimated GFR was calculated by the MDRD (Modification of Diet in Renal Disease)-4 formula.

All included patients had at least one Scr determination before the episode of DI-AIN. The last determination of Scr, obtained 7.5 ± 4.6 (range 0.5–16) months before the onset of DI-AIN, was considered as baseline Scr.

The type of drug responsible for DI-AIN, duration of the treatment, and day of drug withdrawal were carefully recorded. In those patients who received steroids, dosage and duration were also recorded. The highest Scr value registered was recorded, as well as the need for acute dialysis. The intervals between offending drug withdrawal and onset of steroid treatment and between drug withdrawal and performance of renal biopsy were calculated in every patient. Final Scr was defined as the value obtained 6 months after withdrawal of the offending drug. An incomplete recovery of baseline renal function was defined by an Scr value higher than at least 25% of the baseline value.

Patients were divided into two groups according to steroid treatment: Group 1, patients who received steroids and Group 2, patients who were not treated with steroids. In addition, Group 1 patients were subdivided in two groups, according to whether the recovery of baseline renal function had taken place or not (Group 1a, complete recovery of renal function and Group 1b, incomplete recovery of renal function).

Renal biopsy specimens were revised for this study. The severity of interstitial inflammation, interstitial fibrosis was graduated between 0 and $+++$ (absent, mild, moderate, and severe). The percentage of glomeruli showing global sclerosis was recorded.

Statistical analysis

Results are expressed as means ± s.d. For statistical analysis, paired and unpaired tests and non-parametric Mann–Whitney test were used when appropriate. Qualitative variables were analyzed by Fisher's and χ^2-test. Multiple logistic regression analysis was performed to determine the influence of different parameters on the absence of a complete recovery of baseline renal function. Survival analysis were performed with Kaplan–Meier curves and differences estimated by log-rank test. Correlations between quantitative variables were performed with Pearson's correlation coefficient. Statistics were calculated using SPSS for Windows, version 11 (SPSS Inc., Chicago, IL, USA).

DISCLOSURE

The authors state no conflict of interest.

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